TREATMENT AND PREVENTION OF CANCER USING HER3 ANTIGEN-BINDING MOLECULES

[0001] This application claims priority from GB 1913079.8 filed 11 Sep. 2019, the contents and elements of which are herein incorporated by reference for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to the fields of molecular biology, more specifically antibody technology and methods of medical treatment and prophylaxis.

BACKGROUND TO THE INVENTION

[0003] Increased HER3 expression is linked to poor prognosis in multiple solid tumors, including breast, gastric, head & neck, pancreatic, ovarian, and lung cancers. HER3-mediated signalling has adverse consequences for tumour progression; HER3 upregulation is associated with resistance to anti-HER2 and anti-EGFR therapy, and solid tumors refractory to anti-PD-1 therapy have been shown to have higher HER3 expression compared to responders to anti-PD-1 therapy.

[0004] HER3-binding antibodies are described e.g. in Zhang et al., Acta Biochimica et Biophysica *Sinica* (2016) 48(1): 39-48. The anti-HER3 antibody LJM-716 binds to an epitope on subdomains II and IV of the HER3 extracellular domain, locking HER3 in the inactive conformation (Gamer et al., Cancer Res (2013) 73: 6024-6035). MM-121 (also known as seribantumab) has been shown to inhibit HER3-mediated signaling by blocking binding of heregulin (HRG) to HER3 (Schoeberi et al., Sci. Signal. (2009) 2(77): ra31). Patritumab (also known as U-1287 and AMG-888) also blocks binding of heregulins to HER3 (see e.g. Shimizu et al. Cancer Chemother Pharmacol. (2017) 79(3):489-495. RG7116 (also known as lumretuzumab and RO-5479599) recognises an epitope in subdomain I of the HER3 extracellular domain (see e.g. Mirschberger et al. Cancer Research (2013) 73(16) 5183-5194). KTN3379 binds to HER3 through interaction with amino acid residues in subdomain III (corresponding to the following positions of SEQ ID NO:1: Gly476, Pro477, Arg481, Gly452, Arg475, Ser450, Gly420, Ala451, Gy419, Arg421, Thr394, Leu423, Arg426, Gly427, Lys356, Leu358, Leu358, Lys356, Ala330, Lys329 and Gly337), and Met310, Glu311 and Pro328 of subdomain II (see Lee et al., Proc Natl Acad Sci USA. 2015 Oct. 27: 112(43):13225). AV-203 (also known as CAN-017) has been shown to block binding of NRG1 to HER3 and to promote HER3 degradation (see Meetze et al., Eur J Cancer 2012; 48:126). REGN1400 also inhibits binding of ligand to HER3 (see Zhang et al., Mol Cancer Ther (2014) 13:1345-1355). RG7597 (duligotuzumab) is a dual action Fab (DAF) capable of binding to both HER3 and EGFR, and binds to subdomain III of HER3 (see Schaefer et al., Cancer Cell (2011) 20(4):472-486). MM-111 and MM-141 are bispecific antibodies having HER3-binding arms which inhibit HRG ligand binding to HER3 (see McDonagh at al. Mol Cancer Ther (2012) 11:582-593 and Fitzgerald et al., Mol Cancer Ther (2014) 13:410-425).

SUMMARY OF THE INVENTION

[0005] The present invention provides an antigen-binding molecule which is capable of binding to HER3 according to any embodiment described herein, for use in a method of treating or preventing a cancer in a subject, wherein the cancer comprises cells characterised by HER3 ligand expression/overexpression.

[0006] Also provided is the use of an antigen-binding molecule which is capable of binding to HER3 according to any embodiment described herein, in the manufacture of a medicament for use in a method of treating or preventing a cancer in a subject, wherein the cancer comprises cells characterised by HER3 ligand expression/overexpression.

[0007] Also provided is a method of treating or preventing a cancer in a subject, wherein the cancer comprises cells characterised by HER3 ligand expression/overexpression, wherein the method comprises administering a therapeutically or prophylactically effective amount of an antigen-binding molecule which is capable of binding to HER3 according to any embodiment described herein to the subject.

[0008] In some embodiments in accordance with the various aspects of the invention, the cancer comprises cells having a mutation resulting in increased expression of a ligand for HER3.

[0009] More particularly, the present invention provides an antigen-binding molecule which is capable of binding to HER3 for use in a method of treating or preventing a cancer in a subject, wherein the cancer comprises cells having a mutation resulting in increased expression of a ligand for HER3, and wherein the antigen-binding molecule comprises:

[0010] (i) a heavy chain variable (VH) region incorporating the following CDRs: HC-CDR1 having the amino acid sequence of SEQ ID NO:43 HC-CDR2 having the amino acid sequence of SEQ ID NO:46 HC-CDR3 having the amino acid sequence of SEQ ID NO:51; and

[0011] (ii) a light chain variable (VL) region incorporating the following CDRs: LC-CDR1 having the amino acid sequence of SEQ ID NO:91 LC-CDR2 having the amino acid sequence of SEQ ID NO:94 LC-CDR3 having the amino acid sequence of SEQ ID NO:99.

[0012] Also provided is the use of an antigen-binding molecule which is capable of binding to HER3 in the manufacture of a medicament for use in a method of treating or preventing a cancer in a subject, wherein the cancer comprises cells having a mutation resulting in increased expression of a ligand for HER3, and wherein the antigen-binding molecule comprises:

[0013] (i) a heavy chain variable (VH) region incorporating the following CDRs:

[0014] HC-CDR1 having the amino acid sequence of SEQ ID NO:43

[0015] HC-CDR2 having the amino acid sequence of SEQ ID NO:48

[0016] HC-CDR3 having the amino acid sequence of SEQ ID NO:51; and

[0017] (ii) a light chain variable (VL) region incorporating the following CDRs:

[0018] LC-CDR1 having the amino acid sequence of SEQ ID NO:91

[0019] LC-CDR2 having the amino acid sequence of SEQ ID NO:94

[0020] LC-CDR3 having the amino acid sequence of SEQ ID NO:99.